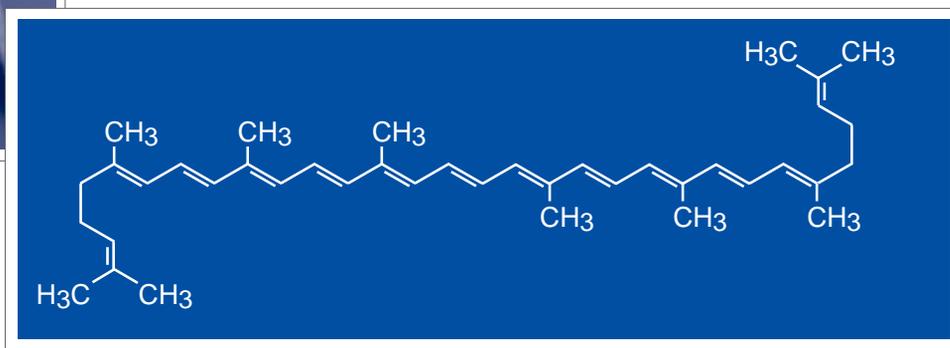


Lycopene

Introduction

Lycopene, a carotenoid without provitamin-A activity, is present in many fruits and vegetables. It is a red, fat-soluble pigment found in certain plants and microorganisms, where it serves as an accessory light-gathering pigment and protects these organisms against the toxic effects of oxygen and light.



Tomato products, including ketchup, tomato juice, and pizza sauce, are the richest sources of lycopene

in the U.S. diet, accounting for greater than 80 percent of the total lycopene intake of Americans.¹ In addition to tomatoes (*Lycopersicon esculentum*) and tomato-based products, lycopene is also found in watermelon, papaya, pink grapefruit, and pink guava. Lycopene from both processed and cooked tomato products is more bioavailable than from fresh tomatoes.²

Dietary intakes of tomatoes and tomato products containing lycopene have been shown in cell culture, animal, and epidemiological investigations to be associated with a decreased risk of chronic diseases, such as cancer and cardiovascular disease.³⁻⁵ In addition, serum and tissue lycopene levels have been inversely correlated with risk of lung and prostate cancers.⁶

Biochemistry and Pharmacokinetics

Lycopene, also known as psi-carotene, is a lipophilic compound, an acyclic isomer of beta-carotene, and is insoluble in water. It is a C40, open-chain carotenoid with 11 conjugated double bonds. Because of the abundance of double bonds in its structure, there are potentially 1,056 different isomers of lycopene, but only a fraction is found in nature.⁷ Lycopene is converted to beta-carotene by the action of lycopene beta-cyclase.⁸

Among the carotenoids, lycopene is found in the serum,⁵ testes, adrenal glands, and prostate.⁴ In contrast to other carotenoids, its serum values are not regularly reduced by smoking or alcohol consumption, although levels are reduced by increasing age.⁹

The linear all-trans configuration is the predominant form of lycopene, making up approximately 90 percent of its dietary sources.¹⁰ Stahl et al found that heating tomato juice resulted in trans-to-cis isomerization of lycopene, and on ingestion the cis isomers of lycopene appeared to predominate in human serum over all-trans isomers.¹¹ Gartner et al showed that more than half of total lycopene in human serum is

in the *cis* form.² The exact functions and relative activities of these different isomers are currently unknown. However, several research groups have suggested *cis* isomers of lycopene are better absorbed than the all-*trans* form.¹⁰ Investigations are currently underway to determine whether there are biological differences between all-*trans* and various *cis* isomers of lycopene regarding its antioxidant properties and other biological functions.¹⁰

Mechanisms of Action

Lycopene has the capacity to prevent free radical damage to cells caused by reactive oxygen species.¹² It is a potent antioxidant *in vitro* and in human studies, reducing the susceptibility of lymphocyte DNA to oxidative damage,¹³ inactivating hydrogen peroxide and nitrogen dioxide,¹⁴ and protecting lymphocytes from nitrogen oxide-induced membrane damage and cell death twice as efficiently as beta-carotene.¹⁴

Evidence is accumulating to suggest other mechanisms of action for lycopene, including modulation of intercellular gap junction communication, an anticancer mechanism.^{5,6} In addition, lycopene at physiological concentrations has been shown to inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression, specifically in prostate cancer cells.⁶

Clinical Indications

Cardiovascular Disease

Lycopene may reduce lipids by inhibiting the enzyme macrophage 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase (an important step in cholesterol synthesis)¹⁵ and by enhancing LDL degradation.¹ In addition, available evidence suggests intimal wall thickness and risk of myocardial infarction (MI) are reduced in persons with higher adipose tissue concentrations of lycopene.¹

Recent epidemiological studies have shown an inverse relationship between tissue and serum levels of lycopene and mortality from coronary heart disease (CHD), cerebrovascular disease,

and MI.¹⁶⁻¹⁸ The strongest population-based evidence on lycopene and MI comes from the European Community Multicenter Study on Antioxidants, Myocardial Infarction and Breast Cancer (EURAMIC) that evaluated the relationship between adipose tissue antioxidant status and acute MI.¹⁶ The study recruited 1,379 individuals (662 patients, 717 controls) from 10 European countries. Needle aspiration biopsy samples of adipose tissue were taken shortly after the infarction, and levels of alpha- and beta-carotenes, lycopene, and alpha-tocopherol were measured. After adjusting for age, body mass index, socioeconomic status, smoking, hypertension, and maternal and paternal history of heart disease, only lycopene levels were found to be protective. The protective potential of lycopene was maximal among individuals with the highest polyunsaturated fat stores, supporting the antioxidant theory. Results also showed a dose-response relationship between each quintile of adipose tissue lycopene and the risk of MI. Similarly, lower blood lycopene levels were also found to be associated with increased risk and mortality from CHD in a concomitant cross-sectional study comparing Lithuanian and Swedish populations.¹⁷

In a recent clinical trial, 60 healthy individuals (30 men/30 women) were randomized to examine the change in plasma lycopene and resistance of lipoproteins to oxidative stress. Fifteen days of tomato product consumption significantly enhanced the protection of lipoproteins to oxidative stress as measured by a significant increase ($p < 0.05$) in the lag period (a measure of antioxidant capacity) after consumption of lycopene.¹⁹

Increased thickness of the intima-media has been shown to predict coronary events.²⁰ Rissanen et al investigated the relationship between plasma concentrations of lycopene and intima-media thickness of the common carotid artery wall (CCA-IMT) in 520 males and females (age 45-69).²¹ The authors conclude that low plasma lycopene concentrations are associated with early atherosclerosis in men, but not women, as manifested by increased CCA-IMT.

Cancer

Oxidative stress is recognized as one of the major contributors to increased risk of cancer, and in chemical assays lycopene is the most potent antioxidant among various common carotenoids.²² Lycopene has been found to inhibit proliferation of several types of human cancer cells, including endometrial, breast, and lung.²³⁻²⁵ In addition, *in vivo* studies have shown lycopene has tumor-suppressive activity.²⁶ Other studies support the hypothesis that carotenoid-containing plant products, such as lycopene, exert a cancer protective effect via a decrease in oxidative and other damage to DNA in humans.²⁷ Lycopene has also recently been shown to elevate levels of hepatic reduced glutathione and biotransformation enzymes, potentially playing a key role in preventing cancer development at extrahepatic sites.²⁸

In one epidemiological review regarding intake of tomatoes, tomato-based products, and blood lycopene levels in relation to the risk of various cancers, 72 studies were identified.²⁹ Of those, 57 reported inverse associations between tomato intake or blood lycopene level and the risk of cancer at a defined anatomic site; 35 of these inverse associations were statistically significant. The evidence for a benefit was strongest for cancers of the prostate, lung, and stomach. Data were also suggestive of a benefit for cancers of the pancreas, colon and rectum, esophagus, oral cavity, breast, and cervix.

Prostate Cancer

Cancer of the prostate is the most commonly diagnosed solid malignancy and the second-leading cause of cancer-related death in men in developed countries.³⁰ A study published by members of the Department of Epidemiology at the Harvard School of Public Health stated, "The strongest known dietary risk factor for prostate cancer is a lycopene deficit."³¹

A number of studies, examining tomato products, lycopene intake, or circulating lycopene levels in relation to prostate cancer risk, suggest high consumption or high circulating concentrations are associated with a reduction in risk of prostate cancer.³²⁻³⁵ In addition, studies have demon-

strated an inverse correlation between dietary lycopene intake and both serum insulin-like growth factor-1 (IGF-1) levels and risk of prostate cancer.³¹ IGF-1 has been shown to play a role in the pathogenesis of prostate cancer;³⁶ therefore, if as proposed, increased serum IGF-1 levels do raise the risk of prostate cancer, lycopene may exert protection against the disease, particularly in its early stages, by decreasing serum IGF-1 levels.³⁷

In a study of lycopene supplementation in males with prostate cancer before radical prostatectomy, Kucuk et al randomized 26 patients to lycopene supplementation (15 mg twice daily) or no supplementation for three weeks prior to surgery.³⁸ In the intervention group 73 percent, compared to 18 percent of the controls, had negative margins ($p=0.02$), and diffuse prostatic intraepithelial neoplasia was seen in 67 percent of the intervention group, compared to 100 percent in the control group. Prostatic-specific antigen (PSA) levels decreased 18 percent in the lycopene group; whereas, they increased 14 percent in the controls. Although the sample size in this randomized study was small, it suggests even a short course of lycopene prior to surgery has the potential to decrease the growth of prostate cancer.

Lycopene at physiological concentrations has also been shown to inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression, specifically in prostate cancer cells, without evidence of toxic effects or apoptosis of cells. Studies using human and animal cells have identified a gene, connexin 43, whose expression is up-regulated by lycopene, allowing direct intercellular gap junction communication (GJC). GJC is deficient in many human tumors and its restoration or up-regulation is associated with decreased proliferation.⁶

Breast Cancer

Some studies have found a significant inverse association between lycopene in breast tissue and breast cancer risk.³⁹ In cell cultures, lycopene has been found to inhibit breast cancer tumors more efficiently when compared to alpha- and beta-carotene.²³

In a case-control study conducted between 1993 and 1999, examining the relationship between 17 micronutrients and breast cancer risk in 289 women with confirmed breast cancer and 442 controls, lycopene was significantly inversely associated with breast cancer risk.⁴⁰ Median intake of lycopene in the “high intake” group was 6.2 mg/day.

In a 1998 study, samples taken from the Breast Cancer Serum Bank in Columbia, Missouri, were analyzed to evaluate the relationship of levels of carotenoids (including lycopene), selenium, and retinol with breast cancer.⁴¹ Only lycopene was found to be associated with a reduced risk for developing breast cancer.

Other Hormone-related Cancers

Intake of dietary lycopene may also play a role in the prevention of ovarian and cervical cancers. From a population-based study of 549 cases of ovarian cancer and 516 controls, researchers estimated the consumption of several antioxidant vitamins and carotenoids, including lycopene, and found lycopene intake was significantly and inversely associated with risk for ovarian cancer, predominantly in postmenopausal women.⁴²

In a multicenter study involving 147 confirmed cervical cancer patients and 191 controls from 1992-1996, lycopene was found to be significantly lower in the cancerous patients.⁴³

In another study involving 32 women with cervical dysplasia (cervical intraepithelial neoplasia (CIN) I, CIN II, and CIN III/carcinoma *in situ*) and 113 controls with normal cervical cytology, women with higher levels of lycopene in the blood were found to have a 33-percent decreased risk of developing cervical cancer.⁴⁴

Lycopene is one of the micronutrients currently being examined in National Cancer Institute-sponsored, phase I, II, or III chemoprevention trials for prostate, breast, and colon cancers.⁴⁵ These studies suggest lycopene may have antiproliferative and chemopreventive properties.

Diabetes

Data from phase I of the Third National Health and Nutrition Examination Survey (1988-1991) were used to examine concentrations of lycopene and other carotenoids in 40- to 74-year-old persons with normal glucose tolerance (n = 1,010), impaired glucose tolerance (n = 277), newly diagnosed diabetes (n = 148), and previously diagnosed diabetes (n = 230), based on World Health Organization criteria.⁴⁶ After adjustment for age, sex, race, education, serum cotinine (a metabolic byproduct of nicotine), serum cholesterol, body mass index, physical activity, alcohol consumption, vitamin use, and carotene and energy intake, lycopene was inversely related to fasting serum insulin after adjustment for confounders (p<0.05). These data suggest a possible role for lycopene in the pathogenesis of insulin resistance and diabetes.

A study investigated the relationship between hyperglycemia and serum carotenoids, including lycopene, and intake of vegetables and fruits. Subjects were recruited with a history of diabetes mellitus (n=133) or with hyperglycemia diagnosed using a conservative 5.6-percent cut-off value for hemoglobin A1c (n=151).⁴⁷ Serum levels of carotenoids and retinol were measured using high-performance liquid chromatography. The authors concluded that an intake of vegetables and fruits rich in carotenoids, including lycopene, might be a protective factor against hyperglycemia.

Other Clinical Indications

Studies have also investigated the relationship and/or use of lycopene for cataracts,⁴⁸ longevity,⁴⁹ malaria,⁵⁰ digestive-tract cancers,^{51,52} immune modulation,⁵³ Alzheimer's disease,⁵⁴ and preeclampsia.⁵⁵ Patients with HIV infection or inflammatory diseases may have depleted lycopene serum concentrations.^{9,56} More clinically oriented research is indicated.

Drug-Nutrient and Nutrient-Nutrient Interactions

Cholesterol-lowering drugs (e.g., probucol),⁵⁷ mineral oil, fat substitutes,⁵⁸ and pectin⁵⁹ may decrease the absorption of lycopene; whereas, beta-carotene,⁶⁰ medium-chain triglycerides, and dietary oils such as olive oil may enhance the absorption of lycopene.⁶¹

Side Effects and Toxicity

Lycopene is generally considered safe, non-toxic, and consumption is usually without side effects. Scientific evidence for lycopene use in pregnancy is not available; however, no adverse events have been reported in association with the consumption of lycopene-containing foods during pregnancy. Obtaining lycopene from food sources, rather than supplements, during pregnancy and while nursing has been suggested.⁶²

Dosage

Therapeutic dosages of lycopene range from 6-60 mg daily. Dosages cited in the literature include 6 mg for reducing the risk of prostate cancer;⁶³ 6.5 mg for reducing the risk of lung cancer in non-smoking women;⁶⁴ 12 mg for reducing the risk of lung cancer in non-smoking men;⁶⁴ 30 mg for decreasing the growth of prostate cancer³⁸ and preventing exercise-induced asthma;⁶⁵ and 60 mg for reducing LDL cholesterol.¹⁵

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